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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF APPEALS

Appln. Serial No.: 09/431,451 | Group Art Unit: 1634

Filing Date: November 1, 1999 | Examiner: Sisson, B.

Applicant: Senapathy, P. | Attorney Docket No.: 34623.005

Title: **METHOD FOR AMPLIFYING SEQUENCES FROM UNKNOWN DNA**

APPLICANT'S BRIEF IN SUPPORT OF APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

On Appeal From Group 1634
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INTRODUCTION

This is an appeal from the Examiner's refusal to allow claims 1-8, 10-12, 14-26, 28, and 29 as set forth in the Final Rejection dated November 13, 2003, and the Advisory Action dated January 8, 2004.

REAL PARTY IN INTEREST

The real party in interest is Genome Technologies, LLC, Madison, Wisconsin, assignee of the entire right, title, and interest in and to the subject application now on appeal, by assignment executed on October 29, 1999, and recorded on December 6, 1999, at reel 10435, frame 694.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1-8, 10-12, 14-26, 28, and 29 are pending in the present application. Each of these claims have been rejected under 35 U.S.C. §102, or, in the alternative, under §103 over Kamb, U.S. Patent No. 5,807,679. Each of claims 1-8, 10-12, 14-26, 28, and 29 are appealed pursuant to the Notice of Appeal filed February 12, 2004.

A copy of the claims on appeal is attached hereto as Appendix 1.

STATUS OF AMENDMENTS

In a first Final Office Action dated June 9, 2003, the Examiner rejected all of pending claims 1-8, 10-12, 14-26, 28, and 29 under §102(e) in view of the Kamb patent. All of the claims were also rejection on obviousness-type double-patenting grounds that are unrelated to this appeal. A copy of the First Final Office Action is attached hereto as Appendix 3.

On July 24, 2003, Appellant filed a first Response After Final pursuant to 37 CFR §1.116, including two statements under 37 CFR §3.73(b) and two Terminal Disclaimers. A copy of the

Response After Final (absent the 3.73(b) Certificates and the Terminal Disclaimers) is attached hereto as Appendix 4.

In a first Advisory Action dated September 4, 2003, the Examiner notified Appellant that the double-patenting rejections had been overcome by Appellant's first Response After Final. The rejection of claims 1-8, 10-12, 14-26, 28, and 29 under §102(e) in view of the Kamb patent was maintained. A copy of the first Advisory Office Action is attached hereto as Appendix 5.

Appellant then filed a Request for Continued Examination (RCE) on September 9, 2003. The RCE included a Preliminary Amendment addressing the continued rejection in view of the Kamb patent. A copy of the Preliminary Amendment is attached hereto as Appendix 6.

The Office mailed a second Final Office Action, dated November 13, 2003. The second Final Office Action rejected all of the now-appealed claims under §102(b), or, in the alternative, §103(a) in view of the Kamb patent. A copy of the second Final Office Action is attached hereto as Appendix 7.

Appellant filed a second Response After Final on November 21, 2003. A copy of the second Response After Final is attached hereto as Appendix 8.

The Office mailed a second Advisory Office Action, dated January 8, 2004. The second Advisory Office Action maintained the rejection of all of the pending claims under §102(b) and/or §103(a) in view of the Kamb patent. A copy of the second Advisory Office Action is attached hereto as Appendix 9.

The present Appeal ensued.

SUMMARY OF THE INVENTION

The invention is a method of **specifically** amplifying only desired regions (such as exons) of a nucleic acid target molecule of unknown sequence using the polymerase chain reaction (PCR) in conjunction with PCR primers of positively defined structure.

Referring to Claim 1, which is representative of the appealed claims, two distinct pluralities of PCR primers are required by the claims, a plurality of first primers and a plurality of second primers. Each primer within the first plurality must include a region of defined nucleotide sequence and a region of randomized nucleotide sequence. Specifically, as set forth

in Claim 1, a region of each first primer is identical to or complementary to a consensus sequence of interest in the nucleic acid target. Another region of each first primer comprises randomized nucleotides (*i.e.*, nucleotides appearing in any sequence). Thus, each first primer includes a region that will match or complement the desired consensus sequence in the target nucleic acid, and a region that is randomized (and may or may not have a complementary sequence in the target nucleic acid).

The plurality of second primers also includes a "fixed" region and a randomized region. However, in the second primers, the region of fixed nucleotide sequence is arbitrary. That is, the fixed region is the same in all of the second primers, but the fixed region does not correspond or correlate to any specific consensus sequence in the target nucleic acid. The fixed region is simply an arbitrary sequence of nucleotides. Each primer in the plurality of second primers also includes a region of randomized nucleotides (in the same fashion as the plurality of first primers).

A nucleic acid target molecule is then subjected to PCR amplification using the first and second pluralities of primers. Of particular note is that the claims require that the nucleic acid regions flanked by the first and second primers are "specifically amplified." See claim 1, clause (c).

As noted in the specification in the "General Approach" section (spanning page 20, line 11, to page 25, line 14), using a first plurality of primers as required in claim 1 ensures that a sub-set of the first plurality of primers will bind "not only to the consensus sequence but also to a few more nucleotides that flank the targeted sequence." See spec., p. 20, lines 26, to p. 21, line 2. Only a sub-set of the first primers will hybridize to the consensus sequence because while each primer has an identical region of fixed sequence, the randomized region is different from primer to primer within the first plurality. As discussed in the specification in at page 21, lines 12-28, when each primer in the plurality of first primers consists of a fixed region 8 nucleotides long, and a randomized region 10 nucleotides long, the plurality of first primers "will contain literally all of the possible one million or so different 10-mer sequences adjacent to the 5' consensus sequence in the human genome." In this fashion, the first plurality of primers functions to prime amplification **not** of the entire target nucleic acid, but only of those portions of the target that are of interest.

The second plurality of primers, which is also partially fixed in sequence and partially randomized, functions to bind to the target at an appropriate distance from the first primers. Together, the plurality of first primers and the plurality of second primers cooperate to prime **specific** amplification of the nucleic acid disposed between the first primers and the second primers. Thus, a key limitation of the present claims is that the portions of the target that are amplifed **are not** arbitrary, random, or non-specific. The claims require that the consensus region of interest be amplified **specifically**. In short, the claims require specific amplificition of only the consensus regions of interest. See the specification, p. 22, lines 3-10, and clause (c) of Claim 1.

As noted page 22, second full paragraph of the specification, the advantage of the claimed invention is that PCR amplification by a full-length primer pair is enabled at each of the consensus sequence locations, although the sequence downstream of a consensus sequence is completely unknown in the nucleic acid target. Within the target nucleic acid, the nucleotides that are downstream, upstream, or on either side of the desired consensus region can be different at each appearance of the consensus sequence within the target nucleic acid. Even so, a particular primer species within the plurality of first primers will bind with full complementarity to any particular consensus site. Therefore, at each of the desired consensus sites in the target nucleic acid, an individual primer from within the plurality of first primers will bind **specifically** and with standard complementarity to the desired consensus sequence.

The plurality of first primers and second primers cooperate to define a primer pair that primes **specific** amplification of the nucleic acid disposed between the locations where the first and second primers bind to the target. The entire target is **not** amplified; only the regions of interest are amplified.

BRIEF DESCRIPTION OF THE REFERENCE CITED BY THE EXAMINER

The single reference relied upon by the Examiner is U.S. Patent No. 5,807,679, issued September 15, 1998, to Kamb. A copy of the Kamb patent is attached hereto as Appendix 2.

The Kamb patent describes a method for determining the **entire** nucleotide sequence of a large DNA molecule. See Kamb, column 4, line 51: "The present invention is directed to determining rapidly the complete sequence of large fragments of DNA."

The Kamb method is known as "island hopping." The term "island hopping" is quite descriptive in that Kamb's approach uses a first step to sequence small regions, or "islands" within the large DNA molecule to be sequenced. Then, in a second step, the **known** sequence of "islands" is used to fabricate perfectly complementary PCR probes to amplify and sequence the DNA situated between the "islands." In this fashion, the **entire** DNA molecule is sequenced by first determining the sequence of a series of "islands" and then "hopping" from island to island (*i.e.*, amplifying and sequencing the DNA "sea" that separates the islands).

Of particular note in the Kamb patent is that the sequence of the "islands" is established using PCR primers that are either **entirely arbitrary in sequence** or PCR primers that include "a unique 5' sequence (**which will later be used as the primer for sequencing reactions**)." See Kamb, column 6, lines 48-61. See also Kamb, col. 7, lines 50-53:

> If the primers used for the PCR had unique 5' ends with degenerate 3' ends, the primers for the sequencing reactions corresponded to the unique portion of the PCR primers.

Thus, in Kamb's approach, the first set of primers used to establish the sequence of the islands **is not** designed to hyubridize to any specific portion of the DNA target. In fact, the exact opposite is true: In Kamb's approach, the first set of primers is **purposefully designed to bind randomly to the target**, thereby elucidating the sequence of a series of randomly situated "islands."

The "unique 5' sequence" in Kamb's first set of primers is not designed *a priori* to bind to a specifically identified sub-sequence within the large DNA target molecule. Rather, the unique 5' sequence in Kamb's first set of primers is used to establish a known priming site within each "island" for purposes of subsequent sequencing of the amplified "islands." Kamb, column 6, lines 50-55. Kamb then uses a second set of PCR primers, **primers that are perfectly complementary to a region within the "islands**," to prime amplification of the unknown "seas" between the now-known "islands." See Kamb, column 8, lines 5-58, especially lines 5-9:

> After analyzing the sequence data of the islands and connecting as many islands as possible into the largest islands possible from this initial set of data, the ends of the islands are used to design new sets of primers to be used in PCR with the primers pointing away from the islands.

Of particular note is that Kamb's approach **does not** prime specific amplification between a desired consensus region of known sequence and some point of unknown sequence removed from the consensus sequence (as is required by the present claims). Instead, in Kamb's first step, the DNA target is amplified completely randomly and the amplified "islands" are then sequenced. In Kamb's second step, the DNA target is amplified **between two or more islands of known sequence**.

ISSUES

Claims 1-8, 10-12, 14-26, 28, and 29 have been rejected under 35 U.S.C. §102, or, in the alternative, under §103 over Kamb, U.S. Patent No. 5,807,679.

Specifically at issue is: (1) whether the Kamb patent anticipates the appealed claims; and (2) whether the Kamb patent renders the appealed claims obvious.

GROUPING OF CLAIMS

For purposes of this appeal, all of claims 1-8, 10-12, 14-26, 28, and 29 will stand or fall together as a single group of claims.

ARGUMENTS

I. THE OFFICE HAS NOT ESTABLISHED A *PRIMA FACIE* CASE OF ANTICIPATION BECAUSE THE KAMB REFERENCE DOES NOT DISCLOSE ALL OF THE LIMITATIONS OF THE PRESENT CLAIMS.

Anticipation is the epitome of obviousness. *In re Grose*, 201 USPQ 57, 61 (CCPA 1979). And it is the Office that bears the burden of establishing a *prima facie* case of obviousness. *In Re Bell*, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). Thus, it is the Office that bears the burden of establishing that the Kamb reference anticipates the present claims.

To establish anticipation, the Office must show that the Kamb reference discloses each and every material element of the present claims. *Studiengesellschaft Kohle, mbH v. Dart Indus.*, 220 USPQ 841, 842 (Fed. Cir. 1984).

The Kamb reference **does not** disclose each and every material element of the present claims.

The Office relies exclusively on the passage from the Kamb patent at column 6, lines 48-56):

> A set of 30 primers is prepared. These primers are matched so that they will work equally well or nearly equally well under the single set of PCR conditions to be used. For example, they may be designed so each has a predicted Tm within a certain narrow range. The primers can be designed each to have a unique 5' sequence (**which will later be used as the primer for sequencing reactions**) and a degenerate 3' sequence **or the primers may simply be individual primers of arbitrary sequence**. (Emphasis added.)

In the first step of the Kamb patent, the primers **are not** designed to amplify any particular region of the target. The primers are designed to amplify the target **randomly**. This is directly contrary to the present claims, which positively require a plurality of first primers that contain a region of fixed nucleotide sequence that is "identical or complementary to a consensus sequence of interest" in the target nucleic acid.

In the Advisory Office Action dated September 4, 2003 (see Appendix 5), the Office responded to this issue by stating that "unique 5' sequence" of Kamb is considered to meet the limitation of a "randomized nucleotide sequence." Appellant assumed this to be a typographical error in that it's clear the Examiner meant to assert that Kamb's "unique 5' sequence" was the same as the "region of fixed nucleotide sequence" in claim 1.

Either interpretation fails to establish anticipation because the "unique 5' sequence" of Kamb's primers is utilized solely "as a primer" **for subsequent sequencing reactions**. See Kamb, col. 7, lines 50-53. The "unique 5' sequence" of Kamb's primers thus **does not** correspond to or complement any specific structure in the target, and do not meet the limitations of claim 1 regarding the nature of the plurality of first primers. In short, Kamb's unique 5' sequence is wholly unrelated to the sequence of DNA target being analyzed.

The present claims, however, explicitly require that the plurality of first primers include a region of fixed sequence that is "identical to or complementary to" a consensus sequence of interest. This aspect of the invention **is not** taught or fairly suggested by the Kamb patent.

Additionally, the present claims require a plurality of second primers having an arbitrary region of fixed sequence and a randomized region. Note that Claim 1 explicitly requires, in step (c) that the nucleic acid template be amplified under conditions wherein the first set of primers binds to the consensus sequence of interest, while the second set of primers binds at locations removed from the consensus sequence so that region between the first and second primers is "**specifically**" amplified.

This is distinctly different than Kamb's approach because in Kamb's approach **all** of the first set of primers bind randomly. Regardless of the configuration of Kamb's first set of primers, **all of them** are designed **in an entirely arbitrary fashion**. The "unique" portion of Kamb's primers **is not** designed to bind to a specific region of the target DNA, but is used solely to insert a sequencing primer location **in the amplified fragments**. The "unique" portion of Kamb's primers has absolutely no relationship whatsoever to the sequence of the target nucleic acid. Again, see Kamb, col. 7, lines 50-53. Kamb makes no attempt to amplify specifically any distinct portion of the target DNA. Kamb's entire approach is focused solely on randomly amplifying and sequencing "islands" in the target DNA, regardless of where the island are situated within the target. (See also pages 2 and 3 of Appellant's Preliminary Amendment attached in Appendix 6.)

Because the Kamb reference fails to teach each and every material limitation of the present claims, Appellant submits that the rejection of claims 1-8, 10-12, 14-26, 28, and 29 under 35 USC §102(b) is improper and should be reversed.

II. THE OFFICE HAS NOT ESTABLISHED A *PRIMA FACIE* CASE OF OBVIOUSNESS BECAUSE THE KAMB REFERENCE DOES NOT SUGGEST OR MOTIVATE ARRIVING AT THE CLAIMED INVENTION.

A. The Office bears the burden of establishing a *prima facie* case of obviousness.

The Office bears the burden of establishing a *prima facie* case of obviousness. *In Re Bell*, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). Precedential opinions from the Court of Appeals for the Federal Circuit have detailed three basic requirements which must be met in order for the Patent & Trademark Office (PTO) to establish a *prima facie* case of obviousness:

1) The prior art must disclose or suggest the modification in the prior art process that is required for the invention, without reference to the Applicant's specification. *Graham v. John Deere Co.*, 148 USPQ 459, 467 (1966); *In Re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

2) The applied reference must convey to one skilled in the art that there is a reasonable expectation of success if the modification is made. *In Re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

3) The reference must provide a "detailed" enabling methodology for practicing the claimed invention. *In Re O'Farrell*, 7 USPQ2d at 1680.

In short:

> It is necessary for the Examiner to present **evidence**, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art **would have been led** to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention." *Ex Parte Levengood*, 28 USPQ2d 1300, 1305 (BPAI 1993) (emphasis in original).

As detailed below, Appellant respectfully submits that the Patent and Trademark Office has not established a *prima facie* case of obviousness against the claims now on appeal because there is no motivation to modify the Kamb patent in the manner asserted by the Office.

B. The Office is reading limitations into the Kamb reference that appear only in Appellant's specification.

In the Second Final Office Action dated November 13, 2003 (attached as Appendix 7), at page 5, paragraph 8, the Office again asserts that Kamb's unique 5' sequence "is considered to

meet the limitation that the [first] primers contain a sequence complementary to the sequence of interest [in the target nucleic acid]." Why?

Kamb certainly does not state that the unique 5' sequence is identical or complementary to a consensus sequence of interest in the target nucleic acid. The only place that limitation appears is in Appellant's own specification and claims. But the Office is not free to use Appellant's own specification to provide the motivation that is lacking in the applied reference.

Contrary to the position taken by the Office, the "unique 5' sequences" of Kamb are entirely arbitrary, random, thoughtless, etc. The "unique 5' sequences" of Kamb **are not** designed (as is the fixed portion of Applicant's primers) to amplify a pre-selected area of the target nucleic acid. As noted earlier, Kamb's primers bind randomly to the target. The "unique 5' sequence" of Kamb is included **solely to provide a known hybridization primer site for subsequent sequencing of the islands**.

Appellants thus submit that this rejection is improper because the Office is relying upon Appellant's own specification to provide the motivation lacking in the applied reference.

C. Modifying Kamb's process to arrive at the claimed invention destroys the stated utility of the Kamb patent.

There is no motivation to modify Kamb's approach to arrive at Appellant's claimed method **because Kamb's stated purpose is to sequence the entire DNA target**, not selected portions of it. On this point there can be no dispute:

> The present invention is directed to determining rapidly **the complete sequence** of large fragments of DNA. (Kamb, column 4, line 51, emphasis added.)

If Kamb's approach were modified so that his "unique 5' sequences" bound only to desired consensus regions of the target DNA, as asserted by the Examiner, the complete sequence of the target **could not, and would not be amplified and thus could not be sequenced**. The stated utility of Kamb's approach would be utterly destroyed.

It is well-settled law that where a proposed modification destroys the utility of the method described in the applied prior art, the rejection is improper. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Thus, the Kamb patent **does not** renders obvious the present claims because

Kamb's amplification protocol is purposefully designed to be non-specific, using random primers, under low-stringency "sloppy" conditions. Kamb's first amplification step **is not** specific as is required by the present claims.

In point of fact, it is the **degenerate** portions of Kamb's primers that control where the primers hybridize, **not** the unique portion. Kamb's primers hybridize randomly throughout the target DNA. These primers are then amplified, thus creating islands. Because the amplified islands then include the "unique sequence" from the first round of amplification, the islands can be extended using the "unique sequence" as a starting point to extend amplification into unknown portions of the target (using standard PCR with a primer fully complementary to the "unique sequence"). In this fashion, the islands are linked to form an entire continent (so to speak). Kamb **purposefully** runs the initial amplification under low stringency conditions so that the resulting "**sloppiness**" generates single-banded, but wholly random, amplification products. See the paragraph in Kamb at column 5, lines 27-50. "Sloppy" amplification is the diametric opposite of "specific" amplification (as required by the present claims).

There is absolutely nothing "specific" about Kamb's approach. And making it specific, as required by Applicant's claims, destroys the stated utility of Kamb's approach. To function, Kamb first amplifies and sequences **random** "islands" within the target DNA, and then amplifies and sequences the "seas" between the "islands" using standard PCR. In this fashion, Kamb sequences **the entire target**. That is Kamb's explicitly stated utility.

But in Appellant's view, sequencing the entire target is a waste of time. Instead, Appellant's claimed invention aims to sequence only the desired parts of the target nucleic acid, those areas that flank a consensus sequence of interest. This approach is wholly distinct from Kamb's approach because Appellant's method **does not** seek to sequence the entire target, but only to amplify **specifically** those portions flanked by the first and second primers, primers which are **purposefully** designed to bind specifically to the target only at regions of interest.

Applicants thus submit that the continued rejection of claims 1-8, 10-12, 14-26, 28, and 29 under 35 USC §103(a) in view of Kamb is improper and should be reversed.

CONCLUSION

In view of the law and facts stated above, it is respectfully submitted to the Board that the Examiner has failed to establish a *prima facie* case of anticipation or obviousness sufficient to support a rejection of the claims under 35 USC §§102(b) and/or 103(a). Absent such a *prima facie* showing, it is respectfully submitted that the Examiner's rejection is untenable and should be reversed.

The Board is therefore respectfully requested to reverse the Examiner's position and to allow claims 1-8, 10-12, 14-26, 28, and 29.

Respectfully submitted,

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APPENDIX 1

CLAIMS ON APPEAL

1. **[AMENDED FOUR TIMES]** A method of amplifying desired regions of nucleic acid from a nucleic acid template comprising:

   (a) providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;

   (b) providing a plurality of second PCR primers, each second primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and then

   (c) amplifying the nucleic acid template via the PCR using the plurality of first PCR primers and the plurality of second PCR primers under conditions wherein a subset of the plurality first primers binds to the consensus sequence of interest substantially wherever it occurs in the template, and a subset of the plurality of second primers binds to the template at locations removed from the first primers such that nucleic acid regions flanked by the first primer and the second primer are specifically amplified.

2. [AMENDED] The method of Claim 1, wherein the template is genomic DNA.

3. [AMENDED] The method of Claim 1, wherein the template is eukaryotic genomic DNA.

4. [AMENDED] The method of Claim 1, wherein template is human genomic DNA.

5. [AMENDED] The method of Claim 1, wherein the template is prokaryotic DNA.

6. [AMENDED] The method of Claim 1, wherein the template is DNA selected from the group consisting of cloned genomic DNA, a subgenomic region of DNA, a chromosome, and a subchromosomal region.

7. [AMENDED] The method of Claim 1, wherein the template is RNA.

8. The method of Claim 1, wherein in step (a) is provided a plurality of first PCR primers, each first primer having a region of fixed nucleotide sequence complementary to a consensus sequence selected from the group consisting of a promoter sequence, a 3' splice sequence, a 5' splice sequence, an Alu repeat, a tandem repeat, poly-A site, a lariat signal, a microsatellite sequence, and a homeobox sequence.

10. The method of Claim 1, wherein in step (a) is provided a plurality of first primers having a G+C content selected from the group consisting of over 50%, under 50%, and about 50%, and in step (b) is provided a plurality of second primers having a G+C content selected from the group consisting of over 50%, under 50%, and about 50%.

11. The method of Claim 1, further comprising step (d): incorporating the amplified fragments of step (c) into a library.

12. **[AMENDED FOUR TIMES]** A method of amplifying exons from a nucleic acid template comprising:

(a) providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence identical or complementary to a consensus sequence of a 3' splice region and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;

(b) providing a plurality of second PCR primers, each second primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence reversely complementary to a consensus sequence of a 5' splice region and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and then

(c) amplifying the nucleic acid template via the PCR using the plurality of first PCR primers and the plurality of second PCR primers under conditions wherein a subset of the plurality first primers binds to a sequence reversely complementary to the 3' splice consensus sequence substantially wherever it occurs in the template, and a subset of the plurality of second primers binds to the 5' splice consensus sequence substantially wherever it occurs in the template, such that exons flanked by the first primer and the second primer are specifically amplified.

14. The method of Claim 12, wherein in step (a) is provided a plurality of first primers having a G+C content selected from the group consisting of cover 50%, under 50%, and at 50%, and in step (b) is provided a plurality of second primers having a G+C content selected from the group consisting of cover 50%, under 50%, and at 50%.

15. The method of Claim 12, further comprising step (d): incorporating the amplified fragments of step (c) into a library.

16. [AMENDED] The method of Claim 12, wherein a genomic DNA template is amplified.

17. [AMENDED] The method of Claim 12, wherein a human genomic DNA template is [specifically] amplified.

18. [AMENDED] The method of Claim 12, wherein a DNA template selected from the group consisting of cloned genomic DNA, a subgenomic region of DNA, a chromosome, and a subchromosomal region is amplified.

19. **[AMENDED FOUR TIMES]** A method of amplifying regions flanking a consensus sequence in a nucleic acid template of totally or partially unknown sequence comprising:

(a) providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;

(b) providing a plurality of second PCR primers, each second primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; then

(c) amplifying the nucleic acid template via the PCR using the plurality of first PCR primers and the plurality of second PCR primers under conditions wherein a subset of the plurality first primers binds to the consensus sequence of interest substantially wherever it occurs in the template, and a subset of the plurality of second primers binds to the template at locations removed from the first primers such that nucleic acid regions flanked by the first primer and the second primer are specifically amplified; then

(d) incorporating the amplified nucleic acid of step (c) into a library;

(e) sequencing a portion of amplified nucleic acid from a particular clone from the library of step (d) and providing a third PCR primer of unique sequence and having an overall length of at least about 10 nucleotides which will prime PCR amplification from the sequenced portion of DNA;

(f) providing a plurality of fourth PCR primers, each fourth primer having an overall length of at least about 10 nucleotides and further having a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and then

(g) amplifying the nucleic acid present in the template via the PCR using the third PCR primer and the plurality of fourth PCR primers under conditions wherein the third primer binds to the sequenced portion of nucleic acid from step (e), and a subset of the plurality of fourth primers binds to the template at locations removed from the third primers such

that nucleic acid regions flanked by the third primer and the fourth primer are specifically amplified.

20. [AMENDED] The method of Claim 19, wherein the template is genomic DNA.

21. [AMENDED] The method of Claim 19, wherein the template is eukaryotic genomic DNA.

22. [AMENDED] The method of Claim 19, wherein the template is human genomic DNA.

23. [AMENDED] The method of Claim 19, wherein the template is prokaryotic DNA.

24. [AMENDED] The method of Claim 19, wherein the template is DNA selected from the group consisting of cloned genomic DNA, a subgenomic region of DNA, a chromosome, and a subchromosomal region.

25. [AMENDED] The method of Claim 19, wherein the template is RNA.

26. The method of Claim 19, wherein in step (a) is provided a plurality of first PCR primers, each first primer having a region of fixed nucleotide sequence identical or complementary to a consensus sequence selected from the group consisting of a promoter sequence, a 3' splice sequence, a 5' splice sequence, an Alu repeat, a tandem repeat, poly-A site, a lariat signal, a microsatellite, and a homeobox sequence.

28. The method of Claim 19, wherein in step (a) is provided a plurality of first primers having a G+C content selected from the group consisting of cover 50%, under 50%, and at 50%, and in step (b) is provided a plurality of second primers having a GC content selected from the group consisting of cover 50%, under 50%, and at 50%.

29. The method of Claim 19, further comprising step (h): incorporating the specifically amplified fragments of step (g) into a library.

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MADISON, WI 537171914

EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/431,451	SENAPATHY, PERIANNAN	
Examiner	**Art Unit**	
Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-12,14-26,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-12,14-26,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 0603 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The finality of the prior Office action is hereby withdrawn.

Information Disclosure Statement

2. Attention is drawn to the Declaration of October 29, 1999 wherein is found the following:

> I acknowledge the duty to disclose information material to the examination of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.
>
> * * *
>
> I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
>
> FULL NAME OF SOLE OR FIRST INVENTOR Periannan Senapathy
>
> INVENTOR'S SIGNATURE P. Senapathy DATE 10-29-99
> Residence: Madison, Wisconsin
> Citizenship: India Post Office Address: 3022 Edenberry Street, Madison, WI 53711

3. It is noted with particularity that the record does not reflect that applicant made the Examiner aware of copending applications nor the issuance of same, nor does the record reflect that applicant made the Examiner aware of prior that was cited in a copending application and which affects the patentability of the instant claims.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. It is noted with particularity that the following rejection was not necessitated by an amendment; however, the prior art cited herein was known to applicant (cited in US Patent 6,521,428 B1) yet not cited in the instant application.

7. Claims 1-8, 10-12, 14-26, 28, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Kamb (US 5,807,679).

8. Kamb, column 6, discloses a method of amplifying nucleic acids using primers that have a length of from 13-30 nucleotides and which can have both a fixed region and a variable region. As et forth in Column 6:

B. Primers for Arbitrary PCR

A set of 30 primers is prepared. These primers are matched so that they will work equally well or nearly equally well under the single set of PCR conditions to be used. For example, they may be designed so each has a predicted T_m within a certain narrow range. The primers can be designed each to have a unique 5 ' sequence (which will later be used as the primer for sequencing reactions) and a degenerate 3 ' sequence or the primers may simply be individual primers of arbitrary sequence. Various lengths of primers can be designed, but it is preferable to use primers of lengths 13–30 nucleotides, more preferably primers of lengths 15–25 nucleotides, and most preferably primers of 15–20 nucleotides. Primers which are 16 nucleotides in length are most commonly used.

The above disclosure is considered to meet the limitation that there be provided a plurality of primers; that the primers be from "about 10 to about 30 nucleotides in length;" and that they contain a 5' region that is randomized as well as a second or non-5' region that is not randomized.

9. Column 6 discloses performing PCR on host DNA that is part of a vector. Column 6 further teaches "[a]ny standard PCR conditions can be used." Such a disclosure is considered to meet the limitation of amplifying genomic eukaryotic and prokaryotic sequence as well as amplifying RNA. Column 1, penultimate paragraph, states that RNA template can be used where one wishes to amplify only exons. The above disclosures are considered to meet the limitation that genomic, chromosomal, and subchromosomal regions can be amplified.

10. The aspect of performing an amplification reaction with said plurality of primers is considered to meet the limitation of generating members of a library and that the amplicons are added to the library.

11. Column 1 discloses research is being conducted into sequencing the genomes of bacteria (prokaryotes), viruses and humans.

12. Column 1 discloses research is being conducted into sequencing the genomes of bacteria (prokaryotes), viruses and humans.

13. The aspect of amplifying nucleic acids that have greater than 50%, less than 50% or 50% G:C content (claims 14 and 28) is considered to fairly encompass all nucleic acids and a such, the nucleic acids amplified by Kamb have as an inherent property just such a G:C content.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

15. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

16. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-8, 10-12, 14-26, 28, and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 11, 12, 16, 19, and 25-29 of U.S. Patent No. 6,521,428 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed method is considered to encompass sequencing reactions ('428 claims 1, 8, 11, 12, 16, and 19) as well as amplifying nucleic acids ('428 claims 25-29).

18. Claims 1-8, 10-12, 14-26, 28, and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 9, and 12 of U.S. Patent No. 6,528,288 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed method of amplifying nucleic acids fairly encompasses the patented method of sequencing by amplification.

Conclusion

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

20. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

23. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
June 7, 2003

Notice of References Cited	Application/Control No. 09/431,451	Applicant(s)/Patent Under Reexamination SENAPATHY, PERIANNAN	
	Examiner Bradley L. Sisson	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,807,679 A	09-1998	Kamb, Alexander	435/6
*	B	US-6,521,428 B1	02-2003	Senapathy, Periannan	435/91.2
*	C	US-6,528,288 B2	03-2003	Senapathy, Periannan	435/91.2
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	09/431,451	SENAPATHY, PERIANNAN	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

All Participants:

(1) *Bradley L. Sisson, Primary Examiner.*

(2) *Joseph T. Leone, Reg. No. 37,170.*

Status of Application: *Finally rejected*

(3) _____.

(4) _____.

Date of Interview: *3 June 2002*

Time: *2:50 PM*

Type of Interview:
- ☒ Telephonic
- ☐ Video Conference
- ☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description:

Part I.

Rejection(s) discussed:
35 USC 103(a)

Claims discussed:

Prior art documents discussed:
US 6,521,428 B1Senapathy (18 February 2003); US 6,528,288 B2 Senapathy (04 March 2003), US 5,807,679 Kamb (15 September 1998)

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

B. L. Sisson
(Examiner/SPE Signature)

(Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed: Mr. Sisson indicated agreement with Mr. Leone as to the request for withdrawal of finality.

Mr. Sisson indicated that issues of obviousness-type double patenting (ODP) exist with respect to two US patents issues this year to applicant, and that prior-art issues may exist with respect to the Kamb patent. Mr. Sisson directed attention to column 6 of Kamb. With respect to the ODP issues, Mr. Sisson indcated that the current clams are broader than that recited in the patents. Mr. Sisson also noted that claims 25-29 of the '428 patent are drawn to a method of amplifying a nucleic acid.

Mr. Leone indicated that he would review the files for both of the Senapathy patents with the thought of preparing a Terminal Disclaimer. Mr. Leone indicated that he would also review the file of the '428 patent for argument relative to the Kamb patent..

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/431,451 Group Art Unit: 1650

Filing Date: November 1, 1999 Examiner: Sisson, B.

Applicant: Senapathy, P. Attorney Docket No.: 34623.005

Title: **METHOD FOR AMPLIFYING SEQUENCES FROM UNKNOWN DNA**

RESPONSE TO FINAL OFFICE ACTION UNDER 37 CFR §1.116

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

To the Commissioner:

In response to the Final Office Action dated June 9, 2003, Applicant respectfully requests favorable reconsideration in view of the following remarks, and entry of the Terminal Disclaimers and Rule 3.73(b) Certification submitted herewith. This Response After Final is submitted within two (2) months from the date of the Final Office Action.

Applicant's Remarks begin on page 2 of this paper.

Two (2) Terminal Disclaimers, the required fee therefor, and two (2) Rule 3.73(b) Certifications accompany this Response After Final.

REMARKS

The following Remarks address the issues presented in the Final Office Action in the order of their appearance:

Applicant's Related Files and the Kamb Reference:

Applicant's undersigned counsel acknowledges, with regret, the failure to advise Examiner Sisson of Applicant's co-pending applications and to provide Examiner Sisson a copy of the Kamb patent, U.S. Patent No. 5,807,679. The failure to provide the Office with all documents material to the prosecution of the subject application, in a timely fashion, rests entirely with undersigned counsel. The omission, however, was unwitting and caused by a procedural lapse. Counsel is reviewing and revising the internal "related files" handling procedures of his office to ensure that a similar lapse does not occur in the future. Counsel regrets the error.

Rejection of Claims 1-8, 10-12, 14-26, 28, and 29 Under §102(e) in View of Kamb (U.S. Patent No. 5,807,679):

This rejection is respectfully traversed because all of the independent claims in the application, Claims 1, 12, and 19, recite that the fixed portion of the first and second pluralities of primers are different from each other; and (2) each primer in the first and second pluralities also includes a randomized portion. Thus, for example, in Claim 1, the first plurality of primers has a region of fixed sequence "identical to or complementary to" a consensus sequence of interest; the second plurality of primers has an arbitrary region of fixed sequence. In all of the present claims, each primer used includes both a fixed portion and a random portion. It is these two pluralities of primers that are then used to amplify the template DNA.

This approach is distinct from the "island hopping" approach described in Kamb. In Kamb's approach, the primers used in the first round of PCR are <u>fully</u> randomized. The primers are then matched pair-wise and each set of pairs is used to prime a separate PCR

reaction. Some of these PCR reactions generate a single locus of amplified DNA, which the Kamb patent calls "islands." It is the "island" DNA that is then sequenced in preparation for a second round of amplification.

Kamb then performs a second PCR reaction, using primers that are explicitly designed (*i.e.* fully fixed in sequence) to anneal specifically to the "island" DNA and to prime amplification leading from the now-known "island" DNA and into the unknown flanking DNA.

Thus, Kamb's approach requires two distinct amplification steps, separated by a sequencing step: a first PCR using fully randomized primer pairs (to generate the "islands"); sequencing of the "island" DNA; and a second PCR using fully fixed primers designed to anneal specifically to the "island" DNA.

This approach is distinctly different from the present approach, where each primer has a fixed-sequence region and a randomized region. A plurality of these primers is then used to amplify the DNA template. As noted above, Kamb approaches the problem using a first PCR with fully random primer pairs; and then follows the first PCR amplification with a second PCR using primers of fully fixed sequence designed to anneal to the "islands" amplified in the first step.

The success of Kamb's approach relies entirely on generating the initial "islands." Once the "islands" are known, Kamb's approach then proceeds using standard PCR, using primers designed to bind specifically to the "islands." This approach is not the same as that currently claimed, nor does Kamb's approach suggest the present claims.

Applicant therefore respectfully submits that the presently claimed invention is neither anticipated by, nor rendered obvious in view of, the Kamb patent. Therefore, withdrawal of the rejection of Claims 1-8, 10-12, 14-26, 28, and 29 under §102(e) in view of Kamb is respectfully requested.

Rejection of Claims 1-8, 10-12, 14-26, 28, and 29 for Obviousness-Type Double-Patenting in View of U.S. Patent No. 6,521,428 B1:

This rejection is rendered moot by the executed Terminal Disclaimer and Rule 3.73(b) Certification submitted herewith. Withdrawal of the same is now requested.

Rejection of Claims 1-8, 10-12, 14-26, 28, and 29 for Obviousness-Type Double-Patenting in View of U.S. Patent No. 6,528,288 B2:

This rejection is rendered moot by the executed Terminal Disclaimer and Rule 3.73(b) Certification submitted herewith. Withdrawal of the same is now requested.

CONCLUSION

Applicant respectfully submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

Joseph T. Leone, Reg. No. 37,170
DEWITT ROSS & STEVENS, S.C.
8000 Excelsior Drive, Suite 401
Madison, Wisconsin 53717-1914
Telephone: (608) 831-2100
Facsimile: (608) 831-2106

I hereby certify that this correspondence is sent by first-class mail, postage pre-paid, in an envelope addressed to:

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Date of Deposit: July 24, 2003

Signature: Marcia Layton

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/431,451	11/01/1999	PERIANNAN SENAPATHY	34623.005	8738

7590 09/04/2003

INTELLECTUAL PROPERTY DEPARTMENT
DEWITT ROSS & STEVENS SC
FIRSTAR FINANCIAL CENTRE
8000 EXCELSIOR DRIVE SUITE 401
MADISON, WI 537171914

EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/431,451	SENAPATHY, PERIANNAN	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 July 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): The obviusnbess-type double patenting rejections.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-8,10-12,14-26,28 and 29*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit: 1634

Continuation of 5. does NOT place the application in condition for allowance because: As presently claimed, and using claim 1 (amended four times) as an example, both the first and second PCR primers can comprised a fixed region as well as a randomized region. Te reproduced portion of column 6 of the '679 patent discloses preparing primers that have a fixed region as well as having a "unique" 5' region. The aspect of a "unique" region is considered to meet the limitation of a "randomized nucleotide sequence." Accordingly, and in the absence of convincing evidence to the contrary, the prior art is considered to fairly teach or suggest the claimed invention.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/431,451 Group Art Unit: 1650

Filing Date: November 1, 1999 Examiner: Sisson, B.

Applicant: Senapathy, P. Attorney Docket No.: 34623.005

Title: METHOD FOR AMPLIFYING SEQUENCES FROM UNKNOWN DNA

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

To the Commissioner:

In response to the Final Office Action dated June 9, 2003, and the Advisory Office Action dated September 4, 2003, Applicant respectfully requests favorable reconsideration in view of the Request for Continued Examination Application and the following remarks

Applicant's Remarks begin on page 2 of this paper.

REMARKS

The following Remarks address the issues presented in the Final Office Action in the order of their appearance:

Rejection of Claims 1-8, 10-12, 14-26, 28, and 29 Under §102(e) in View of Kamb (U.S. Patent No. 5,807,679):

This rejection is respectfully traversed because the Kamb patent describes a two-step process which is patentably distinct from the present claims. The passage at issue from the Kamb patent reads as follows (column 6, lines 48-56):

> A set of 30 primers is prepared. These primers are matched so that they will work equally well or nearly equally well under the single set of PCR conditions to be used. For example, they may be designed so each has a predicted Tm within a certain narrow range. The primers can be designed each to have a unique 5' sequence (which will later be used as the primer for sequencing reactions) and a degenerate 3' sequence or the primers may simply be individual primers of arbitrary sequence. (Emphasis added.)

The difference is that in the first step of the Kamb patent, the primers are not designed to amplify any particular region of the target. The primers are designed to amplify the target randomly. Note that the "unique 5' sequence" of the primers is utilized solely "as a primer" for subsequent sequencing reactions. The "unique 5' sequence" of Kamb's primers thus does not correspond to or complement any specific structure in the target. Nor does Kamb teach or suggest that rather than using the "unique 5' sequence" solely for subsequent sequencing, this portion could be used to specifically amplify a particular region within the target. In short, Kamb utilizes the "unique 5' sequence" of his primers solely to generate priming sites for subsequence sequencing.

In the present invention, however, the claims explicitly require that the first set of primars include a region of fixed sequence that is "identical to or complementary to" a consensus sequence of interest. This aspect of the invention simply is not taught or suggested by the Kamb patent.

Also, the present claims also require a second plurality of primers having an arbitrary region of fixed sequence and a randomized region. Note that Claim 1 explicitly requires, in step (c) that the nucleic acid template be amplified under conditions wherein the first set of primers binds to the consensus sequence of interest, while the second set of primers binds at at locations removed from the consensus sequence so that region between the first and second primers is "specifically" amplified.

This is different than Kamb's approach because in Kamb's approach all of the first set of primer bind randomly. Regardless of the configuration of Kamb's first set of primers, they are designed in an entirely arbitrary fashion. The "unique" portion of Kamb's primers is used solely to insert a sequencing primer location in the amplicons. Even so, Kamb's amplificons are entirely arbitrary. There is no attempt by Kamb to specifically amplify any distinct portion of the template that was selected in advance. Kamb's entire approach is focused solely on amplifying and sequencing unknown stretches of DNA, regardless of where they fall.

It is common knowledge that mammalian DNA contains large stretches of sequence that are uninformative. Rather than taking the time to amplify and sequence all of this uninformative DNA, which is Kamb's approach, the present invention targets only those portions of the DNA template that are of interest.

Thus, Applicants submit that the continued rejection of the claims in view of Kamb et al. is improper. Withdrawal of the same is respectfully requested.

CONCLUSION

Applicant respectfully submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is sent by first-class mail, postage pre-paid, in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Date of Deposit: September 8, 2003

Signature:

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/431,451	11/01/1999	PERIANNAN SENAPATHY	34623.005	8738

7590 11/13/2003

INTELLECTUAL PROPERTY DEPARTMENT
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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/431,451	SENAPATHY, PERIANNAN	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-12,14-26,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-12,14-26,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 September 2003 has been entered.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-8 10-12, 14-26, 28 and 29 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 5,807,679 (Kamb).

6. For convenience, claims 1, 12, and 19, the only independent claims, are reproduced below.

1. **[AMENDED FOUR TIMES] A method of amplifying desired regions of nucleic acid from a nucleic acid template comprising:**
   (a) **providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;**
   (b) **providing a plurality of second PCR primers, each second primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and then**
   (c) **amplifying the nucleic acid template via the PCR using the plurality of first PCR primers and the plurality of second PCR primers under conditions wherein a subset of the plurality first primers binds to the consensus sequence of interest substantially wherever it occurs in the template, and a subset of the plurality of second primers binds to the template at locations removed from the first primers such that nucleic acid regions flanked by the first primer and the second primer are specifically amplified.**

12. [AMENDED FOUR TIMES] A method of amplifying exons from a nucleic acid template comprising:

(a) providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence identical or complementary to a consensus sequence of a 3' splice region and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;

(b) providing a plurality of second PCR primers, each second primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence reversely complementary to a consensus sequence of a 3' splice region and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and then

(c) amplifying the nucleic acid template via the PCR using the plurality of first PCR primers and the plurality of second PCR primers under conditions wherein a subset of the plurality first primers binds to a sequence reversely complementary to the 3' splice consensus sequence substantially wherever it occurs in the template, and a subset of the plurality of second primers binds to the 5' splice consensus sequence substantially wherever it occurs in the template, such that exons flanked by the first primer and the second primer are specifically amplified.

19. [AMENDED FOUR TIMES] A method of amplifying regions flanking a consensus sequence in a nucleic acid template of totally or partially unknown sequence comprising:

(a) providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;

(b) providing a plurality of second PCR primers, each second primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; then

(c) amplifying the nucleic acid template via the PCR using the plurality of first PCR primers and the plurality of second PCR primers under conditions wherein a subset of the plurality first primers binds to the consensus sequence of interest substantially wherever it occurs in the template, and a subset of the plurality of second primers binds to the template at locations removed from the first primers such that nucleic acid regions flanked by the first primer and the second primer are specifically amplified; then

(d) incorporating the amplified nucleic acid of step (c) into a library;

(e) sequencing a portion of amplified nucleic acid from a particular clone from the library of step (d) and providing a third PCR primer of unique sequence and having an overall length of at least about 10 nucleotides which will prime PCR amplification from the sequenced portion of DNA;

(f) providing a plurality of fourth PCR primers, each fourth primer having an overall length of at least about 10 nucleotides and further having a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and then

(g) amplifying the nucleic acid present in the template via the PCR using the third PCR primer and the plurality of fourth PCR primers under conditions wherein the third primer binds to the sequenced portion of nucleic acid from step (c), and a subset of the plurality of fourth primers binds to the template at locations removed from the third primers such that nucleic acid regions flanked by the third primer and the fourth primer are specifically amplified.

7. As seen above, the claimed method requires

providing a plurality of first PCR primers, each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides and further having

Kamb, column 3, discloses performing polymerase chain reaction (PCR). Column 6, lines 56-61, discloses "it is preferable to use primers of lengths 13-30 nucleotides, more preferably primers of lengths 15-25, and most preferably primers of 15-20 nucleotides." Accordingly, the limitation of length is fairly taught by the prior art of record.

8. The claimed methods require the primers to comprise

a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence;

Kamb, column 3, lines 25-26, teaches that his primers "have unique sequences at their 5' ends and degenerate sequences at their 3' ends' are used. Also disclosed is the use of pools of primers. The "unique sequence" is considered to meet the limitation that the primers contain a sequence complementary to the sequence of interest. Kamb, column 3, where it is disclosed that there is a "degenerate sequence at their 3' ends", meets the limitation that the primers also comprise "a region of randomized nucleotide sequence".

Claim 19 requires:

amplifying the nucleic acid present in the template via the PCR using the third PCR primer and the plurality of fourth PCR primers under conditions wherein the third primer binds to the sequenced portion of nucleic acid from step (e), and a subset of the plurality of fourth primers binds to the template at locations removed from the third primers such that nucleic acid regions flanked by the third primer and the fourth primer are specifically amplified.

Kamb, column 8, teaches use of multiple primers pairs , including use of a third and fourth primer, such that multiple nucleic acids of interest are amplified.

9. Kamb, column 3, teaches that "the present invention takes advantage of combining in parallel the power of PCR techniques to increase dramatically the rate of completely sequencing very large fragments of DNA."

10. Column 6 discloses performing PCR on host DNA that is part of a vector. Column 6 further teaches "[a]ny standard PCR condition can be used." Such a disclosure is considered to meet the limitation of amplifying genomic eukaryotic and prokaryotic sequences as well as amplifying RNA. Column 1, penultimate paragraph, states that RNA template can be sued where one wishes to amplify only exons. The above disclosures are considered to meet the limitation that genomic, chromosomal, and subchromosomal regions can be amplified.

11. The aspect of performing an amplification reaction with said plurality of primers is considered to meet the limitation of generating members of a library and that the amplicons are added to the library.

12. Column 1 discloses that research is being conducted into sequencing the genomes of bacteria (prokaryotes), viruses, and humans.

13. The aspect of amplifying nucleic acids that have greater than 50%, less than 50% or 50% G:C content (claims 14 and 28) is considered to fairly encompass all nucleic acids and as such, the nucleic acids amplified by Kamb have as an inherent property just such a G:C content.

14. For the above reasons and in the absence of convincing evidence to the contrary, the invention of claims 1-8, 10-12, 14-26, 28, and 29 are deemed anticipated by the teachings of Kamb, and are therefore rejected under 35 USC 102(b). In the event that Kamb does not anticipate the claimed invention, such disclosure is deemed to render the claimed invention obvious and are rejected under 35 USC 103(a).

Response to argument

15. At page 3 of the response received 15 September 2003 (hereinafter the response), it is asserted that Kamb does not anticipate the claimed invention as the prior art does not teach or suggest having primers that include "a region of fixed sequence that is 'identical to or complementary to' a consensus sequence of interest." This argument has been fully considered and has not been found persuasive. Kamb, column 3, lines 25-26, teaches that his primers "have unique sequences at their 5' ends and degenerate sequences at their 3' ends' are used. The "unique sequence" is considered to meet the limitation that the primers contain a sequence complementary to the sequence of interest. Kamb, column 3, where it is disclosed that there is a "degenerate sequence at their 3' ends", meets the limitation that the primers also comprise "a region of randomized nucleotide sequence". The fact that the primers are identical o complementary to the sequence of interest is evidenced by the amplification of the sequence of interest.

16. Applicant, page 3 of the response, asserts that the claimed invention is further distinguished over the prior art as a second set of primers are required, and these primers also are required to have an arbitrary region of fixed sequence and a randomized region. The preceding

argument has been fully considered and has not been found persuasive. While Kamb does disclose performing PCR with individualized primer pairs, Kamb directs attention to performing PCR with multiple sets of primers that have been combined or "pooled." It is because of this pooling feature/concept that the power of performing PCR in parallel can be achieved. Accordingly, the prior art fairly teaches this limitation.

17. Applicant, page 3, asserts that the primers of Kamb bind in a random manner and that "there is no attempt by Kamb to specifically amplify any distinct portion of the template that was selected in advance." This argument has been fully considered persuasive and has not been found persuasive towards the withdrawal of the rejection for as shown above, the primers of Kamb do result in the amplification of desired sequences. Further, there is no limitation in the claimed method that precludes the presence of additional primers that do not bind to the sequence of interest. As for the claimed method requiring the amplification of known sequences, it is noted that the method of claim 19 seeks to amplify "a nucleic acid sequence template of totally ...unknown sequence." Accordingly, and in the absence of convincing evidence to the contrary, claims 1-8, 10-12, 14-26, 28, and 29 are deemed anticipated by the teachings of Kamb, and are therefore rejected under 35 USC 102(b) or in the alternative, are rejected under 35 USC 103(a).

Conclusion

18. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under

37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

19. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

22. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
07 November 2003

Notice of References Cited	Application/Control No. 09/431,451	Applicant(s)/Patent Under Reexamination SENAPATHY, PERIANNAN	
	Examiner Bradley L. Sisson	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,807,679	09-1998	Kamb, Alexander	435/6
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/431,451 — Group Art Unit: 1650

Filing Date: November 1, 1999 — Examiner: Sisson, B.

Applicant: Senapathy, P. — Attorney Docket No.: 34623.005

Title: **METHOD FOR AMPLIFYING SEQUENCES FROM UNKNOWN DNA**

RESPONSE TO FINAL OFFICE ACTION UNDER 37 CFR §1.116

MAIL STOP: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

To the Commissioner:

Responsive to the Final Office Action dated November 13, Applicant respectfully requests favorable reconsideration in view of the following remarks.

Applicant's Remarks begin on page 2 of this paper.

REMARKS

The rejection of all of the now-pending claims under §102 and/of §103 in view of Kamb, U.S. Patent No. 5,807,679 is respectfully traversed because the Office is not at liberty to disregard the contrary teachings of the applied prior art. Specifically, the Office states, at paragraph 8 of the Final Office Action, that the "unique sequence" as described by Kamb meets Applicant's recited limitation of "a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest." See clause (a) of Claim 1. The Office goes on to note, at paragraph 9 of the Final Office Action, that Kamb uses his disclosed approach "to increase dramatically the rate of completely sequencing very large fragments of DNA." Emphasis added.

This rejection is traversed because the object of the present invention is not "complete sequencing" as taught by Kam. In distinct contrast, the aim and object of the present invention is specific sequencing of only those areas of interest. (This is a positive limitation of Claim 1, which requires, in (c) that the area bounded by the first and second primers be "specifically" amplified.) The "unique sequences" of Kamb are entirely arbitrary, random, thoughtless, etc. The "unique sequences" of Kamb are not designed (as is the fixed portion of Applicant's primers) to amplify a pre-selected area of the target nucleic acid. As noted earlier, Kamb's primers bind randomly to the target. The "unique sequence" of Kamb is included solely to provide a known hybridization primer site for subsequent sequencing.

And this point is absolutely critical: there is no motivation to modify Kamb's approach to arrive at Applicant's claimed method because Kamb's entire stated purpose is to sequence the entire DNA target, not selected portions of it. On this point there can be no dispute:

> The present invention is directed to determining rapidly the complete sequence of large fragments of DNA. (Kamb, column 4, line 51, emphasis added.)

If Kamb's approach were modified so that his "unique sequences" bound only to desired consensus regions of the target DNA, the complete sequence could not, and would not be amplified and thus could not be sequenced. The utility of Kamb's approach would be utterly destroyed. It is well settled that where a proposed modification destroys the utility of

the method described in the applied prior art, the rejection is improper. Thus, the Kamb patent neither anticipates or renders obvious the present claims because Kamb's amplification is purposefully designed to be non-specific, using random primers, under low-stringency "sloppy" conditions. Kamb's amplification **is not** specific as required by the present claims.

In point of fact, it is the **degenerate** portions of Kamb's primers that control where the primers hybridize, **not** the unique portion. Kamb's primers hybridize randomly throughout the target DNA. These primers are then amplified, thus creating islands. Because the amplified islands then include the "unique sequence" from the first round of amplification, the islands can be extended using the "unique sequence" as a starting point to extend amplification into unknown portions of the target (using standard PCR with a primer fully complementary to the "unique sequence"). In this fashion, the islands are linked to form an entire continent (so to speak). Kamb **purposefully** runs the initial amplification under low stringency conditions so that the resulting "**sloppiness**" generates single-banded, but wholly random, amplification products. See the paragraph in Kamb at column 5, lines 27-50.

There is absolutely nothing "specific" about Kamb's approach. And making it specific, as required by Applicant's claims, destroys the stated utility of Kamb's approach. To function, Kamb first creates islands of known sequence, that are then linked via standard PCR to sequence **the entire target**.

But in Applicant's view, sequencing the entire target is usually a waste of time. Instead, Applicant's claimed invention aims to sequence only the important parts of the target, those areas that flank a consensus sequence of interest. This approach is wholly distinct from Kamb's approach because Applicant's method **does not** seek to sequence the entire target, but only to amplify specifically those portions flanked by the first and second primers, primers which are **purposefully** designed to bind specifically to the target only at regions of interest.

Applicants thus submit that the continued rejection in view of the Kamb patent is clearly improper. Withdrawal of the same is respectfully requested.

CONCLUSION

Applicant respectfully submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents,
P.O. Box 1450
Alexandria, VA 22313-1450

Date of Deposit: November 21, 2003

Signature: Marijo J. Jones

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/431,451	11/01/1999	PERIANNAN SENAPATHY	34623.005	8738

7590 01/08/2004

INTELLECTUAL PROPERTY DEPARTMENT
DEWITT ROSS & STEVENS SC
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MADISON, WI 537171914

EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/431,451	Applicant(s) SENAPATHY, PERIANNAN	
	Examiner Bradley L. Sisson	Art Unit 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 November 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-8,10-12,14-26,28 and 29*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit: 1634

Continuation of 5. does NOT place the application in condition for allowance because: The response does not demonstrate that the claimed invention does not encompass the embodiments taught by the prior art of record.

At page 2 of the Rule 1.116 response received 24 November 2003, hereinafter the response, applicant asserts that a point of distinction exists in the size of the nucleic acid to be sequenced. Namely, that the prior art is directed to "completely sequencing very large fragments of DNA" while the claimed invention is asserted to "not" involve complete sequencing, but rather "the aim and object of the present invention is specific sequencing of only those areas of interest." It is noted with particularity that there is nothing that prohibits the "those areas of interest" from being the "very large fragments." Accordingly, applicant is arguing limitations not present in the claims.

At page 2 of the response applicant asserts that another point of distinction resides in the "unique sequence." As stated therein: "The 'unique sequences' of Kamb are not designed (as is the fixed portion of Applicant's primers) to amplify a pre-selected area of the target nucleic acid. As noted earlier, Kamb's primers bind randomly to the target. The 'unique sequence' of Kamb is included solely to provide a known hybridization primer site for subsequent sequencing."

The above argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection. As stated in Claim 1 (four times amended), a "subset" of "first primers" binds not to a "pre-selected area," but rather binds to a "consensus sequence of interest substantially wherever it occurs." Also used is a "second primer" that "binds to the template at locations removed from the first primers." The aspect of being "removed" has been interpreted as being able to bind randomly anywhere else on the template so long that there is at least 1 unpaired template nucleotide between the first and second primers. While Kamb may be able to use their 'unique sequence' in a sequencing method as well, such does not proscribe that same 'unique sequence' from also being capable from binding to a region of interest. The fact that prior art may arrive at the same material steps for different reasons or additional reasons does not make the same steps now patentable.

Accordingly, and in the absence of convincing evidence to the contrary, the rejection is maintained.